First, high dose compositions are neither taught nor suggested by Samo. The doses administered by Samo are relatively small, 0.7 x10^6 units and 2.4 x 10^6 units (or 0.7 x10^5 and 2.4 x 10^5 IU, respectively), as noted in our previous response. Samo also refers to another study where 40 x 10^6 units (or 4 x 10^6 IU) of interferon was administered intranasally. All of the doses either used by or referred to by Samo were significantly lower than the presently claimed compositions. There is no indication that the interferon dose should be increased. In fact, as the following side-by side comparison shows, only at the lowest dose used by Samo is there no pathological response. Thus, one skilled in the art would not be motivated to make the claimed composition, i.e., an ultra-high dose oromucosal IFN composition, based on Samo's nasal spray.

Table 1: Comparison of Samo with the instant invention

	Samo	Samo	Samo	present application
dose (IU)	0.7 x 10^5	2.4 x 10^5	1.0 x 10^6	20 x 10^6
Indicated Use	Anti-viral	Anti-viral	Anti-viral	**Anti-neoplastic**
Pathological Response when administered parenterally	No	Yes	Yes	Yes
Local Adverse Reaction	No	Yes$^+$	Yes*	**No**
Route of administration	Nasal spray	Nasal spray	Nasal spray	**Oromucosal**

$^+$bloody mucus and nasal erosion in ~15% of patients
*nasal irritation, mucosal erosion and blood mixed with mucus in ~26% of patients

Thus, not only did Samo's administration result in approximately 26% of the patients having an adverse response to the IFN but also the route and dosage of IFN administration are not taught or suggested by Samo.

Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the

art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1992). The Samo reference does not contain any teaching, suggestion or motivation to administer IFN either oromucosally or at the ultra-dose claimed in the present invention.

Furthermore, although the Samo reference could be modified to contain an IFN dose falling within the claimed ranges the mere possibility that an increase in dose may be accomplished is insufficient to render obvious the instant invention unless the prior art also suggests the desirability of doing so. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). Interferon possesses known toxicity when administered parenterally. Samo's own data demonstrates that increasing the IFN dose increases the frequency of pathological responses upon parenteral administration. Thus, not only does Samo teach away from the use of ultra-high IFN compositions, Samo fails to provide any suggestion that the ultra-high dose compostions claimed are desirable for oromucosal administration.

Rejection under 35 USC §103 of Claims 6, 13 and 21-33

Claims 6, 13 and 21-33 stand rejected under 35 USC §103(a) as being unpatentable over Cummins et al. Cummins allegedly teaches the oromucosal administration of interferon for treating neoplastic disease and, thus, provides the motivation for the claimed methods and compositions. Applicants respectfully disagrees.

The present invention is directed towards the use of ultra-high doses of interferon in the treatment of neoplastic disease. The doses of IFN administered by Cummins are significantly lower than those used in the present invention. In fact, the dosage of IFN administered by Cummins would fail to elicit a pathological response when administered parenterally and would, thus, not be within the scope of the claimed invention. Moreover, there is no teaching or suggestion that a higher dose be administered and, in view of art recognized toxicity, that a higher dose is desirable.

Applicant notes that the Examiner has invited a side-by-side comparison of the Applicant's invention with Cummins' disclosure. However, it is noted that Cummins data is for humans while the present application contains data for mice. In order to perform an experiment analogous to Cummins the IFN dose to be administered to a mouse would be approximately 0.28 IU [(11 IU/kg)(0.025 kg)]. Applicant has prepared Table 2 presenting a comparison of the data converting the IFN dose (based on weight) given to a mouse to that for a human according to Cummins. As can be seen in the following table, the present invention uses an IFN dose that is 10^4 greater than that disclosed by Cummins.

Table 2: Comparison of Cummins and the present invention

	Cummins	present application
Dosage	11 IU/kg (highest total dose)	**>285,000 IU/kg (lowest total dose)**
Indicated Use	anti-neoplastic	anti-neoplastic
Oromucosal Administration	Yes	Yes
Pathological Response when administered parenterally	No	**Yes**

As noted above, the mere fact that an increase in dose may be possible is insufficient to render obvious the claimed invention unless the prior art also suggests the desirability of doing so. *In re Mills, supra.* Nothing in Cummins suggests or teaches the desirability of increasing the IFN dose.

Conclusion

The instant invention is drawn to compositions and methods of use of ultra-high doses of interferon in the treatment of neoplastic disease. The prior art fails to suggest or teach such a use of ultra-high dose oromucosal interferon or even such an ultra-high dose interferon composition.

The instant invention is directed to an ultra-high dose oromucosal interferon treatment, free of adverse reactions, of a neoplastic disease. First, the inventive composition is for oromucosal

administration. In contrast, Samo administers the interferon via an intranasal route. The oromuscosal environment is significantly different from the nasal environment, e.g., the presence of enzymes in the oromucosal environment. **There is no suggestion in Samo that their intranasal interferon composition should or could be administered oromucosally.**

The Samo reference teaches the use of interferon for the treatment of a viral infection. The present invention is to the treatment of a neoplastic condition. **There is no indication that Samo's composition would be useful in treating a neoplastic condition**. Thus, one skilled in the art would not be motivated to prepare ultra-high dose interferon compositions for the treatment of any disease without eliciting a pathological response, let alone a neoplastic disease.

The Cummins reference teaches an anti-neoplastic use for IFN but the dose is more than 10,000 times lower than what is claimed in the instant application. **There is no teaching or suggestion by Cummins that an ultra-high dose would be desirable or even tolerable in the treatment of a neoplastic condition.**

All rejections having been addressed, reconsideration of the application in view of the foregoing remarks, and an early indication of allowability of Claim 6, 13, and 17 - 33 are earnestly solicited.

Respectfully submitted,

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Date: March 8, 1999

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